

Meeting Report on the International Conference of ECMO-Life Support for Pakistan in 21st Century held May 11-12, 2017, Lahore

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Abstract

Extracorporeal membrane oxygenation support (ECMO) is indicated in severe heart or lung failure with 80 percent or more risk of mortality. In experienced centers, overall survival to discharge ranges from 40 percent in cardiac arrest with extracorporeal cardiopulmonary resuscitation (ECPR) to 70 percent for respiratory failure in adults. Overall survival in children is about 80 percent and newborns with severe lung injury can recover to normal function following prolonged ECMO support, thus, re-defining irreversible lung injury. In the future, ECMO will be automatically controlled with care out of the Intensive care units (ICU) or at home.

The International Conference of ECMO-Life Support for Pakistan in 21st Century which was recently held in Lahore, Pakistan on May 11 - 12, 2017. It was to bring together the best of cardiothoracic and vascular surgeons, heart failure cardiologist, adult and pediatric intensivists, pulmonologists, anaesthetists, cardiovascular nurses, postgraduate trainees, para-medical staff, perfusionists, ambulance cardiac first responders and cardiovascular scientists for thought provoking evidence based discussions on the direction and flow of ECMO technology for Pakistan and the Developing World in the next decade.

The aim of this conference was to share knowledge on ECMO technologies, advancements and their impact on the health capacity building.

Keywords: ECMO; ICU; Pakistan; ELSO

Introduction

Pakistan is a developing country that lacks basic infrastructure for health. Like other developing countries, the implementation of Extracorporeal Life Support (ECMO) is still at an initial stage. CardiacEye International Foundation (CEIF) USA, a humanitarian heart surgery organization, introduced an ECMO network in 2013 manned by a mobile ECMO team to retrieve patients and to attend to patients with critical cardiopulmonary failure refractory to conventional therapy.

Introduction of ECMO through the CEIF significantly raised enthusiasm for the technology in the whole country within the specialty of critical care medicine. The CEIF, despite resource constraints limited mostly to donations from well-wishers introduced the first successful ECMO unit in March 2016. On 19th March 2016, the first case of acute respiratory distress syndrome (ARDS) due to H1N1 influenza was connected to veno-venous ECMO and successfully weaned off after 96 hours. The results were benchmarked against the Extracorporeal Life Support Organization (ELSO) registry and hence, the CEIF was able to secure the ELSO Centre membership for Pakistan.

The CEIF- ECMO center is now working towards training local staff with the Institute of Learning Medicine, Ireland and the University of Health Sciences, Lahore, Pakistan to provide a 24-hours intra-hospital transportation of patients conforming to the relevant international guidelines for multi-organ failure. Summarizing, ECMO will be available for selected cases in healthcare system in Pakistan in the nearest future and will be performed in centres that have done the necessary planning, preparation and training.

Pakistan further faces the specific challenges and opportunities under the midst of overburdened healthcare expectations. With the South-West Asian Chapter (SWAC) of the ELSO Registry, we are hoping to get the platform for the various ECMO programs to be established in this vast and fast developing part of the world to exchange knowledge. The two-day International Conference on ECMO-Life Support for Pakistan in 21st Century May 11-12, 2017 in Lahore, Pakistan conference was one of the efforts in this step.

The Conference retained the most popular features from the other ECMO conferences worldwide, while adding a number of innovations, including;

1. Increased emphasis on implications of ECMO for the developing world;
2. Programs for trainees and young investigators; and
3. New perspectives such as thromboelastography, approaches to data analyses for ECMO patients, role of echocardiography in the structural heart disease, discussion of controversial areas and policy implications.

The content was organized around four domains viz. exposures, outcomes, mechanisms, and interventions display. The format included both plenary and parallel training sessions, with additional special sessions for young perfusionists and opportunities for interdisciplinary discussion.

Hailing from over 10 countries, 300 delegates and participants attended the conference from the United Kingdom, United States of America, Kazakhstan, Tajikistan, Qatar, Kosovo, Moldova, Nigeria, Ireland, Kenya and Kyrgyzstan.

A core planning committee, comprising the authors of this report, was responsible for overall planning and oversight. The core committee had the able assistance of a local organizing committee as well as an at-large planning committee for developing the scientific program, and moderating sessions.

Evidence behind the treatment of ECMO

There were presentations and talks about the subject as ECMO is now considered a recognized treatment for selected patients. The ECMO is being utilized in paediatric settings especially in neonatal heart surgery. ECMO has shown increased survival and reduction in morbidity leading to reduction in longer-term care costs. The utility and futility of ECMO in adults is less clear especially in ARDS [1]. Though studies have shown that ECMO is cost effective and improves survival in adult patients as well. In the last five years many system-

atic reviews covering diverse topics were published. Many authors were unable to find controlled trials hence used level 3 and level 4 [2] evidence from observational studies along with case reports and case series.

It has been suggested that higher volume of patient results in better outcomes and a minimal 22 cases of ECMO per year were recommended [3]. While the review of the literature by MacLaren, *et al.* 2016 [4] reveals that the researchers in different studies and centers were not consistent with their selection of patients. It was noted that some centers might be choosing patients who are very high risk; hence carry higher mortality risk, while other centers showing good recovery rate may be choosing patients' early, carrying lower overall risk. These findings questioned the notion of volume outcome relationship. When in fact it might be the case that better infrastructure with higher competence of the staff may hold the key to better outcomes [4,5].

The importance of consistent application of ELSO guidelines across the centers cannot be over emphasized. Only after this consistent application of selection criteria we could compare and interpret the ECMO registry data meaningfully. ELSO 2013 [6] guidelines state that these guidelines are not standards of care rather just instructions for safe practice of ECMO. This is at odds with standard guidelines produced by other organization, which usually give recommendations based on levels of evidence and based on these levels the authors provide strength of recommendation based on GRADE system [7]. The lack of clarity regarding levels of evidence and strength of recommendations in ELSO Guidelines makes it difficult for practitioners to know exactly how much confidence they can have in a particular guideline recommendation. This issue needs to be resolved as a matter of urgency if consistent application of standards is desired.

The use of ECMO in future is increasing with passage of time [8]. In order to use the ECMO appropriately; we have to make sure that following critical issues are taken care of:

- Choosing the right patient at right time.
- Adherence with the ELSO guidelines.
- Having the right team (well trained and experienced).
- Having the robust clinical audits and data assessments.
- Applying the standards consistently.
- Centralization of services.
- Provision of ECMO transport facility.
- Development of guidelines based on latest evidence
- Strength for Each recommendation should be provided based on GRADE system.

Rehabilitation for ECMO Patients

The forum also discussed the role of rehabilitation in the ECMO patients. Prolong length of stay in hospital is a well-recognized cause of neuromuscular weakness and impaired physical functioning. For such critically ill patients, physical therapy (PT) has been demonstrated to be safe and effective treatment during the stay. The impact of such an intervention on patients receiving ECMO is remarkable to improve the quality of life. Early mobilization with physical therapy may decrease duration of hospitalization as well as psychological wellbeing. Physical therapy decreased the developing complication during the prolonged bed rest e.g. muscle atrophy, contracture, bedsores, deconditioning and poor long-term outcome [9,10]. But, not all the patients are suitable for the early mobilization there is some contraindication also. Yet it needs competent team dynamics and collaboration, proper screening and troubleshooting select suitable candidates. Exercise tolerance may vary day to day. Mobilization should be carefully done. The objectives of the meeting for the rehabilitation talks were

- a. To improve the frequency of rehabilitation consultations and treatments to improve patients' functional mobility before and after ECMO.
- b. To reduce the functional immobility of the patients during long length of stay in ICU.

ICU Management during ECMO

As the meeting proceeded to the next day, comprehensive discussions commenced on the management of the ECMO patients. The intensive care management and the success of the ECMO therapy depend not only on device flow, overall gas exchange but also on patient's hemodynamics and avoidance of complications. The delegates discussed the management of a patient on ECMO in ICU. Though it is a tedious but important task and involves vigilant monitoring with prompt actions to resolve the issues. It was discussed that to accomplish this one should have an insight of the process and should know what to monitor where to look for the problem and how to trouble shoot. Monitoring of such patients comprises of taking care of circuits, blood flow, heart rhythm, mean arterial pressure, gas exchange, organ perfusion, oxygen delivery, temperature regulation, anticoagulation, limb ischemia, bleeding and infection. The presentations at the conference specifically focussed on ICU management of ECMO patients including all aspects of patient's hemodynamics, mechanical determinants of blood flow, factor affecting gas exchange, arterial blood pressure and monitoring of oxygen delivery [11,12].

Haematology and Thromboelastography during ECMO

There was an exclusive session arranged for the Thrombelastograph Analyzer (TEG). TEG is used to monitor the ability of the patients blood to clot. Haemostasis is an active, extremely complex process, involving many interacting factors including clotting, fibrinolytic proteins, activators, inhibitors and cellular elements.

TEG can reduce the need for transfusions during ECMO by predicting how a patient's blood will clot. The TEG analyzes the platelets resistance or inhibition there by reducing drug intervention and blood product usage. Some reports have shown that by reducing exposure to blood, you reduce length of stay and mortality rates in high blood loss surgeries (i.e. open-heart surgery). The TEG can also accurately assess low molecular weight Heparin and Coumadin, and has the ability to distinguish surgical bleeding from non-surgical bleeding [13,14].

Biomaterials Compatibility; Consideration in ECMO

One of the exciting talks was on the use of the ECMO to replace the lungs' gas exchange capacity in refractory lung failure. However, the duration of application is dependent to a large degree on the biomaterials compatibility properties. The synthetic materials were initially developed for industrial use because of their excellent physical properties and only later adapted for biomedical use. Thus, all these synthetic materials, their application in medicine display more or less the same disadvantage: an incompatibility with blood and tissues. Through contact with the blood, this incompatibility can provoke a pathophysiological response from the organism, similar to that of traumatic shock (septic shock).

When blood comes into contact with artificial surfaces of the ECMO circuit typically composed of plasticized polyvinyl chloride (PVC) blood tubing, oxygenator gas exchange membranes, and cardiectomy reservoir, it leads to an immediate triggering in blood of the so-called "contact activation systems". These are host defense mechanisms that are programmed to isolate and if possible destroy a foreign substance or surface which the blood 'sees'. The contact between blood and artificial surfaces of the extracorporeal system results in non-specific "post-perfusion syndrome". To ameliorate these negative side effects several techniques have been developed to improve biomaterials compatibility. In addition, the speaker further suggested that two approaches have been adapted so far;

- a) Surface modification with bioactive substances.
- b) Pharmacological inhibition of the key enzymes responsible for the consecutive activation of the cascade reactions.

This presentation provided an insight into the new kind of surface modification technologies available that can commonly be applied to biomaterials to improve biocompatibility and therefore the longevity and ECMO safety.

ECMO as bridge to Transplant

Then, there was a frank panel discussion on the presentation of ECMO as a bridge to transplant. It was presented that mortality of patients awaiting organ transplant remains a significant problem as the number of patients on the waiting list far surpasses the number of

donor organs available. Interest in the use of ECMO as a bridge to organ transplant has emerged. ECMO support for end-stage pulmonary disease or the failing heart has been extensively used as a bridge to organ transplantation in both adults and paediatric patients when it is the only viable therapeutic option left for patients on transplant waiting list. Unfortunately, ECMO is associated with many known complications, including thromboembolic events, bleeding, immobilization, infection, end-organ dysfunction, and risk of neurological impairment. Recent developments in techniques and devices have not only enabled patients to benefit from ECMO, but also have led to decreases in the risk of complications associated with prolonged mechanical ventilation. The presentation provided a summary of evidence on the role of ECMO as a bridge to heart and lung transplantation which has garnered greater interest in the field of transplantation, especially for ventilation-refractory patients.

ECMO is a life support technology which although has been used for over 40 years yet is still evolving. A general consensus exists for its use in neonates and children with reversible cardiorespiratory failure. Its widespread use in adults is lately being recommended with evidence from the CESAR trial. There remain monumental challenges with its rationale use. Integration of this technology into the existing ICU infrastructure should be seamless. Various modalities and the challenges will be discussed in this extensive review. Participants were taken through the basic physiological principles of ECMO, oxygen delivery protocols, ABG interpretation in various modes, various ventilation strategies, monitoring of the patients, trouble shooting if something goes wrong, weaning protocols and the challenges that the physicians would face in the ICU.

Emerging Research in ECMO- Oxidative stress

The initiation of ECMO is associated with an immediate and complex oxidative stress, similar to that seen in systemic inflammatory response syndrome (SIRS) [15]. At that moment when the patient's blood first comes into contact with the foreign surface of the extracorporeal circuit, a variety of coagulative and inflammatory cascades are activated. Levels of pro-inflammatory cytokines rise rapidly, which, in association with activation of the complement and contact systems, results in leukocyte activation [16]. This innate immune response, if severe, persistent or unchecked by a compensatory anti-inflammatory response (CARS) [17], may lead to endothelial injury, disrupted microcirculation, and end-organ dysfunction [16,17]. Despite major improvements in pump and circuit design, oxygenators and the advent of heparin-bonded surfaces, the oxidative stress response to ECMO remains a clinical concern. While a large volume of work has been directed towards elucidating and targeting the inflammatory response to cardiopulmonary bypass (CPB) [18], a closely related form of extracorporeal circulation, much less has been devoted to studying the inflammatory response to ECMO.

Other Aspects

With the automation and servo regulation in place, there will be a need for ECMO specialists as the supervising team, educators, and management of the circuit and emergencies. It will become standard practice to have 10 or 20 patients on ECMO in any given hospital at any given time, including the full spectrum of ages and cardiac and respiratory support. For adult respiratory support management of ECMO in the ICU will be as routine as managing a patient on a ventilator or on renal replacement therapy is today. While most adult patients are on ECMO for 7 - 14 days, a significant fraction of patients will be on ECMO for a month or more awaiting lung recovery or perhaps transplantation. These patients are quite stable and can be managed in step-down units. The fact that there may be several patients with respiratory failure on ECMO for a month or more will result in the establishment of regional lung failure centers which are equipped to manage a dozen or more chronic ECMO patients at a time, bridging to transplantation or to recovery. These units will be similar to the heart failure centers now common practice in major medical centers. ECMO patients will be managed in conventional hospital settings or perhaps even at home with appropriate monitors and alarms. This will be similar to the management of patients with ventricular assist devices at home which has evolved over the last 15 years.

Implantable membrane lungs are membrane devices attached by conduits directly to the circulation, either to the heart directly or to peripheral vessels. The membrane lungs themselves will be paracorporeal, attached to the access cannulas that pass through the skin. The reason for this is that the devices will have to be changed from time to time and, although they could be implanted subcutaneously or in

the pleural space, the need for evaluation and replacement makes the paracorporeal position the most convenient for long term support. These implantable lungs may be used for bridging to transplantation and as destination therapy for end stage lung disease in patients who are not candidates for transplantation. Implantable membrane lungs can be used without the need for blood pumps, relying either on pulmonary artery pressure or systemic arterial pressure to drive blood through the device. As destination therapy these devices will be used first for palliation of severe COPD. Because the goal is primarily CO₂ removal, the devices can be small in size and have a relatively small gas exchange surface area.

The application of the devices and techniques described above will result in the next generation of ECMO management. The characteristics of advanced ECMO will be awake, extubated, spontaneously breathing patients, without systemic anticoagulation, managed in step-down units, general care or even at home.

The Future

An inherently interdisciplinary field, ECMO has benefited greatly from different congresses to date, as they bring together, under one roof, the many scientists and clinicians who otherwise would not have the opportunity to share their research with those from other fields. It is clear that the incorporation of ECMO therapy into our existing healthcare system is expensive. It was suggested at the closing remarks that rather than using the mobile, portable and customized systems as depicted by some big companies and prevalent mostly in Middle East, we should rely on more commonly used centrifugal pumps and non-customized circuits and common monitoring systems like in USA and Europe. Combined with this strategy, we should be able to reduce the cost of the ECMO therapy. We should initiate and develop an exchange program for technology transfer among the meeting participating countries. Build up a common data base from the respective countries and then collate it under the ELSO charter. And, develop common curriculum under the ELSO charter and training program and examination system.

At the closing of the conference, a declaration was passed to establish a society of ECMO for Developing World, with a proposed name "The ECMO Society of Developing World (ESDW). With this society, all the participating countries could plan annual ECMO conferences in partner countries; start the Society Journal for publication of manuscripts; and develop curriculum under the ELSO Society guidelines with common examination, training system and research programs.

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